REVIEW ARTICLE

# Vaccination Safety Update

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## SUMMARY

Introduction: In Germany, a large number of biased reports against vaccination have recently been published in all of the news media, and particularly on the internet. This paper discusses the safety profile of modern vaccines and their continuous surveillance and shows why the current criticism of vaccination on safety grounds is unjustified.

Methods: The authors have performed a selective literature search to enable a proper distinction to be drawn between scientifically justified and unjustified reports on the potential adverse effects of vaccination.

Results: At present, the safety of a new vaccine must be demonstrated in large-scale clinical trials before the product is licensed. After licensing, the safety of new vaccines is constantly monitored, and the results of monitoring are published.

Discussion: An examination of these data reveals that the expressed doubts about the safety of vaccines are unjustified.


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**Key words: vaccination, side effects, safety, surveillance, unjustified scepticism about vaccines**

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Vaccination is the most effective medical primary prevention measure. The efficacy and utility of vaccination in controlling widely feared infectious diseases is convincingly demonstrated by the eradication of smallpox and the successful combating of poliomyelitis and diphtheria. In 1930s Germany around 6000 people, most of them children, died annually of diphtheria and a further 500 succumbed to poliomyelitis. Thanks to vaccination, these diseases have now disappeared from Germany. The risks of vaccination must be seen alongside its benefits. It goes without saying that the adverse effects of a vaccine must not exceed acceptable limits, i.e., a vaccine may not inflict lasting damage on the vaccinee's health.

## Licensing and batch testing

A new vaccine is licensed for use only after exhaustive testing. Only when its efficacy and safety have been demonstrated in a multi-stage test procedure (*table 1*) a national license is granted by the German Federal Agency for Sera and Vaccines – the Paul-Ehrlich-Institut.

At European Union (EU) level the European Medicines Agency in London (EMEA; http://www.emea.europa.eu) is responsible for licensing new vaccines. Details of the EU legal framework for regulation of pharmaceutical products can be found on the internet (http://ec.europa/eu/enterprise/pharmaceuticals/index_en.htm).

Licensing alone does not mean that a vaccine can be distributed in Germany. Batch testing and batch release by the Paul-Ehrlich-Institut is required. The same is true at EU level: the EMEA is responsible for licensing procedures, while the provisions for batch testing and release are regulated by a central institution in Strasbourg, the European Directorate for the Quality of Medicines and Health Care (EDQM; http://www.edqm.eu/site/page_628.php).

## Monitoring of side effects and complications

Despite painstaking clinical testing, at the time of licensing of a vaccine the clinical experience is limited. Even if the tests involve several thousand probands, very rare side effects (<1:10 000) and long-term effects may emerge only after the product has been licensed. Thus, the safety of vaccines must be monitored after licensing.

German law (§ 6 Abs. 1 Nr. 3 IfSG) requires specific reporting of all after-effects of vaccination that go beyond the usual vaccine reaction. Definitions of usual and unusual reactions to vaccines were published by the German Standing Vaccination Committee in 2004 and updated in 2007 (1) (*table 2*).

Whenever such a reaction is suspected, the physician is obliged to report it immediately to the local Health Office on the standard preprinted form (www.pei.de/cln_047/nn_158140/DE/infos/fachkreise/meldeformulare-fach/meldeformulare-fachnode.html?__nnn=true, accessed 23.7.2007). The Health Office forwards the pseudonymized registration form to the Paul-Ehrlich-Institut. The collection and evaluation of these reports at the Paul-Ehrlich-Institut (e1–e4) is crucial to the early recognition of danger signals. Potential risks are publicized (www.pei.de) and, if it is deemed advisable, investigated in clinical and epidemiological studies. If unacceptably severe side effects are established, the vaccine is removed from the market. An example of this is provided by the withdrawal of a vaccine against tickborne encephalitis in March 2001.

Apart from this legal duty to report suspicious cases, the physician has a professional obligation to report suspected vaccine side effects to the Drug Commission of the German Medical Association (www.akdae.de).

The existence of compulsory registration and the fact that German law provides for compensation for damage to health by an officially recommended vaccination (§ 60 IfSG) underline the high importance accorded by the state to protection of its population by vaccination and to the guarantee of safety to the individual vaccinee.

## The objections of vaccination skeptics

On the internet, in books, in informal meetings and even at symposia, one can hear critical voices warning of the alleged risks of widespread administration of vaccines. This section presents the current state of knowledge with regard to various specific criticisms of vaccination.

### Hypothesis: "Mercury contained in vaccines harms brain growth"

For many decades thimerosal has been added to vaccines as a decontaminant. It has been used millions of times in vaccinations all over the world. Thimerosal is an organic mercury compound and is degraded in the body to ethyl mercury. In the 20th century the human mercury burden increased threefold owing to the burning of fossil fuels and garbage incineration (e5). Prenatal exposure to high levels of mercury, particularly through maternal consumption of contaminated fish, is said to impair fetal neurological development (e6).

The fear that the brain development in young infants might be damaged by vaccines containing thimerosal was misplaced. Inadmissibly, the ethyl mercury burden was derived from guidelines for methyl mercury (2). Investigations in apes and in humans have shown that these two substances display notable differences in their pharmacokinetics. Ethyl mercury has a considerably shorter elimination half-life (e7). To date the only reported problems after administration of thimerosal-containing vaccines have been hypersensitivity reactions, which cannot be described in terms of an illness (e8).

Following the recommendation of the EMEA (3), all vaccines for use in children are now free of thimerosal.

### Hypothesis: "Hepatitis B vaccine causes multiple sclerosis or triggers a flare"

Ever since the introduction of hepatitis B immunization, fears have been expressed that the vaccination causes multiple sclerosis (MS) or accelerates the progression of the disease. For this reason, several epidemiological studies have been carried out in recent years (5, e9–e12). With the sole exception of one case-control study (4), none of these investigations has shown a significant risk of MS or any other demyelinating disease following hepatitis B virus (HBV) vaccination.

This case-control study (4) was criticized by the WHO (6) for methodological deficiencies, e.g., too small a sample. A detailed statement can be found on the homepage of the Paul-Ehrlich-Institut (e13). Another study with a very similar design (5) showed no significantly increased risk of MS in persons vaccinated with HBV (odds ratio 0.8, 95% confidence interval [CI] 0.4 to 1.4).

### Hypothesis: "Measles vaccination causes or favors autism"

A publication in The Lancet (e13) made a connection between measles vaccination and gastrointestinal symptoms and developmental disorders (7). This led to widespread anxiety in Great Britain regarding the safety of the measles-mumps-rubella (MMR) vaccines. The heated debate between critics and proponents of vaccination continues to the present day.

On February 20, 2004 The Lancet described this study as "flawed" by a "fatal conflict of interest" and stated that it should never have been published. In the meantime the British medical authorities are preparing to revoke the principal author's license to practice medicine, on suspicion of corruption.

According to an official statement from the Institute of Medicine, a causal link between MMR vaccination and autism can now be excluded, on the basis of a meta-analysis (8).

In Germany doubts over measles vaccination persist. "Measles parties" have even been organized (e15), with the intention that healthy children should be infected by a child with measles and acquire "natural immunity". Regional outbreaks of measles, sometimes with serious complications, are the result (e16).

### Hypothesis: "Mumps vaccination, Haemophilus influenzae type b vaccination, and hepatitis B vaccination cause autoimmune diseases such as type 1 diabetes"

A link between diabetes mellitus type 1 and mumps vaccination has been postulated from time to time (10, e17–e19), but it is now clear that the vaccination does not cause type 1 diabetes (11, e20). At one point Finnish investigators (9, e21) raised the same suspicion against Haemophilus influenzae type b (Hib) vaccination;

**TABLE 1**

**Clinical testing of vaccines**

| | |
|---|---|
| Phase I | Careful assessment of tolerance and immunogenicity in a small population (<100) |
| Phase II | Dose finding and tolerance (several 100 probands) |
| Phase III | Consistency of industrial production procedures; confirmation of tolerance and immunogenicity (several thousand probands) and proof of efficacy (several 1000 probands) in randomized controlled trials, in the absence of known serologic surrogate parameters for immune protection |
| Phase IV | Further investigation of particular aspects in connection with the licensed indications, epidemiological studies, monitoring of use or safety studies after licensing |

**TABLE 2**

**After-effects of vaccination exceeding the normal reaction**

| Symptom | Frequency | Delay from vaccination to occurrence | Duration | Cause/vaccine antigen | Remarks |
|---|---|---|---|---|---|
| Febrile convulsions | Few per thousand | 4 to 72 h (inactivated vaccine) 7 to 14 days (live vaccine) | Minutes | Immaturity of child's temperature regulation (all recommended vaccinations in critical age span) | At age <5 years; no lasting damage |
| Hypotonic hyporesponsive episode (HHE) | < 1 : 1 000 | Minutes to 2 days | Minutes | All vaccines for basic immunization | No lasting damage |
| Arthralgia/ arthritis | Few percent | 7 to 30 days | Weeks | Immune complexes after rubella or hepatitis B vaccination (rare) | Spontaneously reversible |
| Thrombocytopenia | < 1 : 10 000 | 7 to 30 days | Weeks | After MMR or varicella vaccination | Spontaneously reversible |
| Neuritis | Isolated cases | 5 to 42 days | Weeks/months | Various vaccines | Spontaneously reversible |
| Polyneuritis, polyradiculitis | Isolated cases | 5 to 42 days | Weeks/months | Various vaccines | Spontaneously reversible |
| Anaphylaxis (shock) | Extremely rare | Within 30 minutes, max. 24 h | Minutes | Type I allergy, all vaccines | Emergency treatment |
| Anaphylactoid reaction (shock) | Extremely rare | Minutes | Minutes | Mediator release after intravasal injection, all vaccines | Emergency treatment |
| Guillain-Barré-syndrome (GBS) | 1:1 Mio. | 5 to 42 days | Weeks/months | Molecular mimicry or bystander activation, influenza vaccination | Reversible |
| Apnea | Few percent | Minutes to 72 h | Seconds | In babies born prematurely (<28 to 30 weeks' gestation), immaturity of respiratory center | Monitoring |

however, a painstaking meta-analysis (12) demonstrated no causal connection.

It has also been discussed whether vaccinations might either directly cause or trigger other autoimmune diseases, such as rheumatic disorders and lupus erythematosus. To date, studies with level of evidence III have shown no unfavorable effect of vaccinations for influenza (e22), hepatitis B (e23), meningococci C (e24), or MMR (e25) on the course of idiopathic juvenile arthritis. Nevertheless, further studies should be conducted into the safety and immunogenicity of vaccinations in such diseases (e26).

#### Hypothesis: "Vaccinations can transmit pathogens"

It is sometimes conjectured that vaccines might transmit pathogens such as HCV or HIV (13). In the 1980s, for example, this accusation was made against hepatitis B vaccine, which was derived from the plasma of hepatitis B antigen carriers. However, the literature contains no single mention of such a case. Furthermore, hepatitis B vaccine is now produced solely by gene technological means.

Protein-containing adjuvants are present in culture media and thus are found in trace quantities in vaccines. They have been discussed as a possible risk factor, particularly with regard to bovine spongiform encephalitis (BSE), a few cases of which are still occurring in Europe (e27). Vaccines can be viewed as BSE-safe, however, and their BSE safety is rigorously controlled by the Paul-Ehrlich-Institut (14). All protein-containing vaccine additives are tested accordingly.

#### Hypothesis: "Multiple vaccinations overload/weaken the immune system"

A question frequently raised by vaccination skeptics is whether a child's immune system might not be overburdened (15), particularly by combined vaccines comprising up to 25 different antigens (e28). In humans, however, the T-cell receptors responsible for the recognition of microbial antigens are present in quantities on the order of $10^{18}$ even in childhood (16). On today's knowledge of the immune system, the antigens in combined vaccines occupy only a minute fraction of the available receptors.

#### Hypothesis: "Vaccines promote allergies"

In the early 1990s the incidence of atopic diseases and infections in children was significantly higher in Western Germany than in the eastern part of the country, the previous GDR (17, e29). This is explained by the "hygiene hypothesis". In simplified form, this states that microbial stimulus of the Th1 immune system results in reduction of the Th2 system, responsible for atopy (e30). The prevention of infectious diseases could lead to upgrading of the Th2 system and thus to an increase in allergies (e19).

If this hypothesis were valid, however, the frequency of atopy in the old GDR, with its high vaccination rate, should have been much higher. Both the process of postnatal immune maturation and the findings of recent clinical studies speak against the hypothesis. Plainly vaccines, like infections, act as Th1 stimuli.

The most important impetus for postnatal immune maturation is provided not by infections or vaccinations, however, but by the natural bacterial colonization in the first few days of life. This takes place primarily in the gut (e31).

Investigators specifically seeking an influence of infections and vaccinations on the frequency of atopy have found a moderate (e32) or marked (e33–e35) reduction in the risk of atopy, but never an increase.

#### Hypothesis: "Vaccines can trigger fits (epilepsy)"

This criticism of vaccination arose in the 1960s and 1970s. In the wake of the postvaccinal encephalitis (e38, e39) that had followed vaccination against smallpox, there was widespread fear of an equally serious wave of postvaccinal encephalopathy after whole-cell pertussis vaccination (18, e36, e37, e39).

Wide-ranging epidemiological studies (19, 20, e40) and detailed differential diagnostic investigations (21) show that modern vaccines can cause high febrile reactions with febrile convulsions (e41, e42). These occur relatively infrequently with the acellular vaccines used in Germany, but are fairly common with the whole-cell pertussis vaccine used around the world. However, a large study on more than 600 000 children (22) has excluded any possibility of a febrile convulsion progressing to fits or triggering epilepsy. Retrospectively investigated children suffering from fits showed a lower frequency of previous pertussis vaccination than healthy children without fits.

In this regard, a mutation was found of the SCN1A gene, which is normally responsible for neuronal sodium transport. The demonstration of this mutation in 11 of 14 children with severe myoclonic epilepsy who were suspected of having vaccinal encephalopathy suggests a genetic disorder rather than an adverse effect of vaccination (e43).

#### Hypothesis: "Sudden infant death syndrome is connected with vaccinations, particularly with hexavalent vaccines"

In recent years deaths in the first and second years of life soon after vaccination with hexavalent vaccines have attracted much publicity (23). With regard to deaths in the first year of life, there was no sign of an increased risk of sudden infant death syndrome (SIDS). An association was found between one of the two hexavalent vaccines and sudden unexpected death (SUD) in the second year of life, in that the number of deaths reported was higher than would normally have been anticipated.

However, this connection was based on only four cases. In the meantime the vaccine has been withdrawn from the market for other reasons. Its hepatitis B antigen content is apparently being reconsidered and may be raised if deemed necessary.

In the industrialized nations, SIDS is known to be the most frequent cause of death in infants after the end of the neonatal period. One of the defining characteristics

of SIDS, besides the sudden death of a healthy child in his/her sleep, is age between six weeks and four months. This is the period when every infant receives the standard vaccinations, so an incidental association is preprogrammed. Several studies, recently also in Germany, have looked into the possibility of increased risk. Venemann et al. (24) showed in repeated investigations, culminating in a meta-analysis (25), that the odds ratio for sudden infant death in a univariate analysis was 0.54 (95% CI 0.39 to 0.76). Although the heterogeneity of the studies demands caution in interpreting the findings, one has to ask whether vaccinations might not actually protect against SIDS.

Since August 2005 the Robert Koch Institute (Berlin) has been running the TOKEN Study, examining deaths in children aged 2 to 24 months. The aim of this study is to identify previously unknown risk factors for early death. These may include certain living conditions, problems during pregnancy or birth, illnesses, and medical or medicinal treatment, including vaccinations. Further information on this wide-reaching three-year study can be found on the internet (http://www.rki.de/nn_201180/DE/Content/GBE/Erhebungen/WeitereEpiStudien/TOKEN__Studie/token__node.html?__nnn=true, accessed on 23.07.2007).

## Conclusions

The currently marketed vaccines meet high standards of safety.

Numerous new vaccines have recently been licensed for use. A few examples are:

- Rotavirus vaccines
- Vaccines to protect against cervical cancer (human papillomavirus vaccines)
- Measles-mumps-rubella-varicella combined vaccines
- Vaccine to protect against herpes zoster and postherpetic neuralgia
- Influenza vaccine from tissue culture and many more

Further novel vaccines are undergoing clinical testing:

- Improved conjugate vaccines to protect against pneumococcal and meningococcal infections
- Live attenuated influenza vaccines
- Malaria vaccines
- Japanese encephalitis vaccines

All these vaccines have to be proved safe as well as effective, not only before but also after they are licensed for use.

The most important instrument for early recognition of danger signals is passive monitoring. All physicians are called on to report every suspicion of complications following vaccination without delay, to further strengthen the foundations for scientific evaluation of the safety of modern vaccines.

**Conflict of interest statement**
The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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